Roark, Jessica

From: Gambel, Phillip
Sent: Wednesday, July 30, 2003 8:17 AM
To: STIC-ILL
Cc: Roark, Jessica
Subject: cancer models limitations

stic

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_____murine cancer models _____

17/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13903145 BIOSIS NO.: 200200531966
SCID mouse models to study human cancer pathogenesis and approaches to therapy: Potential, limitations, and future directions.
AUTHOR: Bankert Richard B(a); Hess Stephen D(a); Egilmez Nejat K(a)
AUTHOR ADDRESS: (a)Department of Microbiology, State University of New York at Buffalo, 3435 Main Street, 138 Farber Hall, Buffalo, NY, 14214**USA
E-Mail: rbankert@buffalo.edu, sdhess@hotmail.com, negilmez@buffalo.edu
JOURNAL: Frontiers in Bioscience 7 (Cited May 17, 2002):pc44-c62 May 1, 2002
MEDIUM: online
ISSN: 1093-4715
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The successful engraftment of human tumors and human immunocompetent cells into severe combined immunodeficient (SCID) mice has led to the generation of a wide array of different experimental designs that have proven useful in studying the cell biology of human cancer, and for evaluating novel therapeutic approaches to the treatment of cancer. In this review five of the most frequently used embodiments of the SCID model are presented. The goals of this review are to discuss how each model has been utilized to study human cancer and its response to many different novel therapies, to provide an assessment of the strengths and limitations of each model, and to outline future directions with a focus on what is needed to overcome some of the current limitations and pitfalls of the SCID models.

_____murine cancer models _____

17/7/30 (Item 30 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
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03084813 BIOSIS NO.: 000020027932
USEFULNESS AND LIMITATIONS OF MURINE TUMOR MODELS FOR THE IDENTIFICATION OF NEW ANTI TUMOR AGENTS
AUTHOR: GOLDIN A; JOHNSON R K; VENDITTI J M
AUTHOR ADDRESS: OFF. INTERNATL. TREATMENT RES., DIV. CANCER TREATMENT, NATL. CANCER INST., BLDG. 31, RM. 10A-22, BETHESDA, MD. 20014, USA.
JOURNAL: MIHICH, E. AND S. ECKHARDT (ED.). ANTIBIOTICS AND CHEMOTHERAPY, VOL. 28. DESIGN OF CANCER CHEMOTHERAPY: EXPERIMENTAL AND CLINICAL APPROACHES. X+192P. S. KARGER: BASEL, SWITZERLAND; NEW YORK, N.Y., USA. ILLUS. ISBN 3-8055-0411-X. 0 (0). 1980. P1-7. 1980
CODEN: ANBCB
RECORD TYPE: Citation
LANGUAGE: ENGLISH

murine cancer models

17/7/37 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2003 Elsevier Science B.V. All rts. reserv.

11421375 EMBASE No: 2001435714
The history and rationale for monoclonal antibodies in the treatment of hematologic malignancy
Dillman R.O.
R.O. Dillman, Hoag Cancer Center, One Hoag Drive, Newport Beach, CA 92658 United States
AUTHOR EMAIL: rdillman@hoaghospital.org
Current Pharmaceutical Biotechnology (CURR. PHARM. BIOTECHNOL.) (Netherlands) 2001, 2/4 (293-300)
CODEN: CPBUB ISSN: 1389-2010
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 86

The potential of antibodies as "magic bullets" for cancer therapy has been appreciated for nearly a century. During the past 25 years, various scientific developments have made possible the production of unlimited quantities of clinical-grade murine, chimeric, and humanized monoclonal antibodies (MoAbs). Intact, unconjugated MoAbs may: [1] produce anticancer effects through the immune system on the basis of interactions between the Fc portion of antibody and complement proteins and/or effector cells; [2] induce regulatory effects by neutralizing circulating ligands or blocking cell membrane receptors, thereby interfering with ligand/receptor interactions and signal transduction; [3] serve as immunogens for anti-cancer vaccines through the anti-idiotype-network cascade. Conjugated MoAbs can serve as carriers of other agents such as radioisotopes, natural toxins, chemotherapy drugs, cytokines, and immune cells. Important aspects of the antigenic target are the degree to which it is tumor-specific or tumor-associated, whether it internalizes or not, whether it is shed, the density of expression, and the physiologic significance of the antigen to the target cell. The clinical foundation for antibody-mediated therapy was laid in the 1980s when investigators established the safety of antibody administration, defined certain predictable antibody-mediated toxicities, and confirmed that antibodies could reach tumor targets and produce antitumor effects. A major limitation of these early mouse monoclonal antibodies was overcome with the production of antibodies with varying degrees of humanization. In 1997 rituximab (RituxanSUP(R)), a mouse-human chimeric anti-CD20, became the first MoAb approved by

regulatory agencies for the treatment [redacted] human malignancy.

_____murine cancer models _____

17/7/38 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
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11383772 EMBASE No: 2001397084
Building 'validated' mouse models of human cancer
Hann B.; Balmain A.
B. Hann, Cancer Research Institute, Mount Zion Comprehensive Cancer Ctr., University of California, San Francisco, CA 94143-0875 United States
AUTHOR EMAIL: abalmain@cc.ucsf.edu
Current Opinion in Cell Biology (CURR. OPIN. CELL BIOL.) (United Kingdom) 01 DEC 2001, 13/6 (778-784)
CODEN: COCBE ISSN: 0955-0674
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 68

As a model system for the understanding of human cancer, the mouse has proved immensely valuable. Indeed, studies of mouse models have helped to define the nature of cancer as a genetic disease and demonstrated the causal role of genetic events found in tumors. As the scientific and medical community's understanding of human cancer becomes more sophisticated, however, limitations and potential weaknesses of existing models are revealed. How valid are these murine models for the understanding and treatment of human cancer? The answer, it appears, depends on the nature of the research requirement. Certain models are better suited for particular applications. Using novel molecular tools and genetic strategies, improved models have recently been described that accurately mimic many aspects of human cancer.

_____murine cancer models _____

17/7/40 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
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11152626 EMBASE No: 2001167186
The mouse in cancer research; past, present, future(?)
Hunter K.; Cozma D.
K. Hunter, Laboratory of Population Genetics, DCEG/NCI/NIH, 41 Center Drive, Bethesda, MD 20892 United States
AUTHOR EMAIL: Hunterk@mail.nih.gov
Current Genomics (CURR. GENOMICS) (Netherlands) 2001, 2/1 (1-26)
CODEN: CGUEA ISSN: 1389-2029
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 240

The mouse has long been an important component of cancer research. From the realization by Little and Bagg early days of the past century demonstrating a heritable component of sponanteous cancer to the oncogenic manipulations of the germline today, the mouse has been and will continue to be the major mammalian in vivo system to study neoplasic transformation and progression. Use of the mouse has pervaded almost every aspect of cancer research, including discovery of oncogenes, analysis of tumor suppressors, development of novel therapeutic strategies, and exploring the mutagenic effects of chemicals and ionizing radiation, to name a few. The development over the last twenty years of transgenic, homologous recombination and conditional-transgenic or knockout technologies has

enormously expanded the breadth and scope of the mouse in cancer research and has contributed significantly to our understanding of the events that lead up to and accompany neoplastic transformation. Although there are significant limitations of modeling human cancers in the mouse, these proven technologies as well as technologies currently under development, will continue to provide experimentally tractable systems in which to explore the genetic and molecular events of cancer initiation and progression. As a result, the mouse as a model for human neoplastic disease will continue to have a significant place in the experimental toolbox of cancer researchers for many years to come.

_____murine cancer models _____

17/7/50 (Item 17 from file: 73)
DIALOG(R)File 73:EMBASE

04497939 EMBASE No: 1990389467
Principles of tumor immunology: Lessons from animal models
Kripke M.L.
Department of Immunology, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030 United States
Immunology and Allergy Clinics of North America (IMMUNOL. ALLERGY CLIN. NORTH AM.) (United States) 1990, 10/4 (595-606)
CODEN: INCAE ISSN: 0889-8561
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Much of the knowledge concerning tumor antigens and tumor immunity is derived from experiments with laboratory rodents. This article deals with the findings and limitations of early studies on tumor specific transplantation antigens. It includes a discussion of more recent studies of UV-induced skin cancers and murine melanomas and presents some of the new findings from basic immunology relevant to tumor immunology.

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Fr m: Gambel, Phillip
Sent: Wednesday, July 30, 2003 8:03 AM
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Subject: costimulatory antibodies cancer

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---------- costimulatory antibodies ----------

7/7/4 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

07528290 EMBASE No: 1998413577
Modulating the immune response to genetic immunization
Cohen A.D.; Boyer J.D.; Weiner D.B.
D.B. Weiner, 505 Stellar-Chance Bldg., Department of Pathology, Univ. of PA School of Medicine, 422 Curie Blvd., Philadelphia, PA 19104 United States
AUTHOR EMAIL: dbweiner@mail.med.upenn.edu
FASEB Journal (FASEB J.) (United States) 1998, 12/15 (1611-1626)
CODEN: FAJOE ISSN: 0892-6638
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 110

Genetic immunization, also known as DNA or polynucleotide immunization, is a novel strategy for vaccine development in which plasmid DNA encoding either individual or a collection of antigens is directly administered to a host. Such immunization leads to host expression of the delivered foreign gene, resulting in the induction of a specific immune response against the in vivo produced antigen. DNA immunization has been shown to induce protective immune responses in several infectious disease and cancer experimental model systems. Furthermore, DNA vaccines have recently entered the clinic for analysis as both prophylactic and therapeutic agents. Although the mechanisms of immunity to DNA have not yet been fully elucidated, it has become apparent that the immune response achieved by DNA vaccination is quite malleable, and can be manipulated by altering the conditions under which the vaccine is administered. Either through changing the method or location of immunization, altering the number of immunostimulatory sequences in the plasmid, altering the immunization regimen, or coadministering genes for cytokines or costimulatory molecules, one can modulate both the magnitude and orientation of the subsequent immune response. Through maximization of this feature of DNA immunization, we will likely be able to design vaccines and immunotherapeutic agents that are tailored to the correlates of

protection for a particular disease, resulting in a new generation of more focused and effective immune stimulating agents.

---------- costimulatory antibodies ----------

12348414 BIOSIS NO.: 200000101916
Vaccination against human cancers (Review).
AUTHOR: Sinkovics Joseph G(a); Horvath Joseph C
AUTHOR ADDRESS: (a)Cancer Institute, St. Joseph's Hospital, 3001 W. Dr. ML King Jr. Blvd., Tampa, FL, 33607**USA
JOURNAL: International Journal of Oncology 16 (1):p81-96 Jan., 2000
ISSN: 1019-6439
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Classical and molecular immunological means of active tumor -specific immunization against human cancers yielded 'crude' whole cell or tumor cell lysate vaccines of preventive value (reduced relapse rates) and dendritic cell-peptide or genetically engineered vaccines that may induce remissions even in metastatic disease. Active tumor-specific immunization was often successful in the past 50 years against experimental tumors maintained in the laboratory. During the epochs of classical and molecular immunology several vaccines were generated and used for the reduction of relapse rates of human cancer after surgical removal of the primary or metastatic tumors. Whole cell vaccines consist of X-irradiated autologous or allogeneic tumor cells coadministered with immunostimulants (BCG, Detox). Tumor cells haptenized biologically (as in viral oncolysates) or chemically were also used. Dendritic cell vaccines are prepared by transfection or transduction with tumor antigen-encoding DNA or by pulsing the cells with antigenic peptides in vitro; or collecting dendritic cells that engulfed apoptotic tumor cell DNA and/or peptide antigens in vivo for reinjection into the patient. Genetically engineered tumor cells are prepared in vitro to express MHC and peptides, costimulatory molecules (B7.1) and cyto- or lymphokines (interferons, interleukins, hematopoietic growth factors) for vaccination of patients. Antibody- and immune T cell-mediated immune reactions to autologous tumor cells are newly generated and/or quantitatively increased in immunized patients but do not always correlate with clinical response. Most vaccines are claimed to have reduced relapse rates presumably by inducing effective host immunity against micrometastases. Dendritic cell-peptide vaccines could induce partial or occasionally complete remissions in metastatic disease. The wrong antigenic presentation may result in tolerance induction toward the tumor; occasionally tumor enhancement may occur. Human tumor antigens when presented appropriately (with costimulatory molecules and with IL-2, IL-12) break the host's natural tolerance toward its tumor and induce rejection strength immune reactions even in patients with metastatic disease. Immune T cells thus generated could be collected for adoptive immunotherapy. For successful active specific immunization against human cancers the understanding of the immunoevasive maneuvers of the tumor cell (through FasLfwdarwFas; TRAIL; CD40LfwdarwCD40; TGFbeta etc. systems) is essential.

---------- costimulatory antibodies ----------

10/7/1 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

10992919 EMBASE No: 2001035557
CpG DNA increases primary malignant B cell expression of costimulatory molecules and target antigens
Jahrsdorfer B.; Hartmann G.; Racila E.; Jackson W.; Muhlenhoff L.; Meinhardt G.; Endres S.; Link B.K.; Krieg A.M.; Weiner G.J.
Dr. G.J. Weiner, University of Iowa Cancer Center, 5970Z JPP, University of Iowa, Iowa City, IA 52242 United States
AUTHOR EMAIL: george-weiner@uiowa.edu
Journal of Leukocyte Biology (J. LEUKOCYTE BIOL.) (United States)
2001, 69/1 (81-88)
CODEN: JLBIE ISSN: 0741-5400
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 46

Multiple factors, including expression of costimulatory molecules, antigen-presenting molecules, and target antigens, likely impact the efficacy of antibody therapy and other approaches to the immunotherapy of B cell malignancy. Unmethylated CpG-dinucleotides in select base contexts ("CpG motifs") that resemble sequences found in bacterial DNA are potent immunostimulatory agents capable of inducing a complex immune response, including a strong B cell stimulus. We examined the effect of a potent human CpG oligonucleotide (CpG ODN 2006) on different types of primary human malignant B cells and reactive follicular hyperplasia. CpG of oligodeoxynucleotide (CpG ODN), but not control (non-CpG ODN), increased the expression of costimulatory molecules (CD40, CD80, CD86, CD54) on malignant B cells without altering the phenotype of B cells obtained from reactive follicular hyperplasia. CpG ODN also enhanced expression of class I and class II MHC in most samples. CD20 expression was increased in response to CpG ODN, most notably in B-CLL and marginal zone lymphoma. An inverse correlation was found between baseline expression of CD20 and CD40 and their expression after exposure to CpG ODN, thus the most significant increase in expression of these molecules was found in those samples that had the lowest baseline levels. In conclusion, CpG ODN can lead to increasing expression of molecules involved in co-stimulation , antigen presentation, and as targets for antibody-based therapy and deserve further evaluation as potential immunotherapeutic agents for B cell malignancy.

---------- costimulatory antibodies ----------

9/7/53 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09557267 21338758 PMID: 11445125
Pathways for self-tolerance and the treatment of autoimmune diseases.
Goodnow C C
Australian Cancer Research Foundation, Genetics Laboratory, Medical Genome Centre, John Curtin School of Medical Research, Australian National University, Canberra, Australia.
Lancet (England) Jun 30 2001, 357 (9274) p2115-21, ISSN 0140-6736
Journal Code: 2985213R

Document type: Journal Article; Re ; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Antigen delivers both immunogenic and tolerogenic signals to lymphocytes. The outcome of antigen exposure represents a complex integration of the timing of antigen binding with signals from many other immunogenic and tolerogenic costimulatory pathways. A road map of these signalling pathways is only beginning to be charted, revealing the mechansim of action and limitations of current immunotherapeutic agents and the points of attack for new agents. Ciclosporin and tacrolimus interfere with tolerogenic signals from antigen in addition to blocking immunogenic signals, thus preventing active establishment of tolerance. Corticosteroids inhibit a key immunogenic pathway, NFkappaB, and more specific inhibitors of this pathway may allow tolerance to be actively established while immune responses are blocked. New experimental therapies aim to mimic tolerogenic antigen signals by chronically stimulating antigen receptors with antigen or antibodies to the receptor, or aim to block costimulatory pathways involving CD40 ligand, B7, or interleukin 2. Obtaining the desired response with these strategies is unpredictable because many of these signals have both tolerogenic and immunogenic roles. The cause of autoimune diseases has been determined for several rare monogenic disorders, revealing inherited deficiencies in tolerogenic costimulatory pathways such as FAS. Common autoimmune disorders may have a biochemically related pathogenesis. (52 Refs.)

Record Date Created: 20010710
Record Date Completed: 20010726

---------- costimulatory antibodies ----------

9/7/52 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09766912 21571738 PMID: 11714839

Augmentation versus inhibition : effects of conjunctional OX-40 receptor monoclonal antibody and IL-2 treatment on adoptive immunotherapy of advanced tumor.

Kjaergaard J; Peng L; Cohen P A; Drazba J A; Weinberg A D; Shu S
Center for Surgery Research and Lerner Institute, Cleveland Clinic Foundation, Cleveland, OH 44195, USA.

Journal of immunology (Baltimore, Md. - 1950) (United States) Dec 1 2001, 167 (11) p6669-77, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: R01 CA78263; CA; NCI; R01 CA89511; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Therapeutic efficacy of adoptive immunotherapy of malignancies is proportional to the number of effector T cells transferred. Traditionally, exogenous IL-2 treatment has been used to promote the survival and function of transferred cells. Recently, we described the therapeutic effects of in vivo ligation of the costimulatory receptor, OX-40R, on activated T cells during early tumor growth. In this study, we examined the effects of IL-2 and OX-40R mAb on adoptive immunotherapy of advanced tumors. For treatment of 10-day 3-methylcholanthrene 205 pulmonary metastases, systemic transfer of 50 x 10(6) activated tumor -draining lymph node T cells resulted in >99% reduction of metastatic nodules. With either IL-2 or OX-40R mAb conjunctional treatment , only 20 x 10(6) cells were required. Advanced 10-day

3-methylcholanthrene 205 intracran[redacted]umors could be cured by the transfer of 15 x 10(6) L-selectin(low) T cells derived from draining lymph nodes. In this situation, IL-2 administration inhibited therapeutic effects of the transferred cells. By contrast, 5 x 10(6) T cells were sufficient to cure all mice if OX-40R mAb was administrated. Studies on trafficking of systemically transferred T cells revealed that IL-2, but not OX-40R mAb, impeded tumor infiltration by T cells. Tumor regression required participation of both CD4 and CD8 T cells. Because only CD4 T cells expressed OX-40R at cell transfer, direct CD4 T cell activation is possible. Alternatively, OX-40R might be up-regulated on transferred T cells at the tumor site, rendering them reactive to the mAb. Our study suggests OX-40R mAb to be a reagent of choice to augment T cell adoptive immunotherapy in clinical trials.
Record Date Created: 20011120
Record Date Completed: 20020102

---------- costimulatory antibodies ----------

9/7/50 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09986734 21913132 PMID: 11916305
Effective tumor immunotherapy: start the engine, release the brakes, step on the gas pedal,...and get ready to face autoimmunity.
Tirapu Inigo; Mazzolini Guillermo; Rodriguez-Calvillo Mercedes; Arina Ainhoa; Palencia Belen; Gabari Izaskun; Melero Ignacio
Gene Therapy Division, Facultad de Medicina and Clinica Universitaria, Universidad de Navarra, Pamplona, Spain.
Archivum immunologiae et therapiae experimentalis (Poland) 2002, 50 (1) p13-8, ISSN 0004-069X Journal Code: 0114365
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Cellular immune responses can destroy cancer cells, achieving the cure of experimental malignancies. An expanding wealth of knowledge on the molecular basis of how to prime and amplify a T cell response has fueled a number of strategies successful at treating established tumors (rather than merely preventing tumor grafting). The most efficacious approaches operate at different stages, including: 1) priming the immune response using tumor antigen-expressing dendritic cells or tumor cells transfected with genes that render them immunogenic, 2) sustaining and amplifying immunity using agonistic monoclonal antibodies against costimulatory molecules or immune-potentiating cytokines, and 3) eliminating mechanisms that self-regulate the strength of the immune response, such as inhibitory receptors or regulatory T cells. A rational combination of such approaches holds great hope for cumulative and synergistic effects, but there is also evidence that they can open the flood-gates for unwanted inflammatory reactions. The next decade can be envisioned as the time when the first reproducibly efficacious combination regimes for cancer immunotherapy will become available and widely used in the clinic, as clinicians learn the best strategies and try to harness their potentially damaging effects. (62 Refs.)
Record Date Created: 20020327
Record Date Completed: 20021004

---------- costimulatory antibodies ----------

9/7/39 (Item 22 from file: 73)
DIALOG(R)File 73:EMBASE

06958872 EMBASE No: 1997243440
Role of costimulation in tumor immunology
Kabelitz D.
D. Kabelitz, Dept. of Immunology, Paul-Ehrlich-Institute, D-63207 Langen Germany
AUTHOR EMAIL: kabelitz@em.uni-frankfurt.de
Cancer Journal (CANCER J.) (France) 1997, 10/3 (157-161)
CODEN: CANJE ISSN: 0765-7846
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 53

Two signals are required for efficient activation of T-lymphocytes. Signal one is provided by antigen recognition through the CD3-associated T-cell receptor (TCR). Signal two is delivered from costimulatory B7 molecules expressed on antigen-presenting cells to the corresponding receptors (CD28) on the surface of T-lymphocytes. In the absence of signal two, T-cells become anergic and do not mount an efficient cellular immune response. Tumor cells frequently lack the expression of B7.1 (CD80) and/or B7.2 (CD86) molecules and are therefore unable to provide costimulatory signals to potentially tumor-reactive T-lymphocytes. In several instances, the immunogenicity of tumor cells has been successfully increased by transfection of genes coding for B7.1 or B7.2. While the B7 counter-receptor CD28 mediates positive costimulation of T-lymphocytes, the alternative B7 counter-receptor CTLA4 (CD152) is a negative regulator of T-cell activation. Blockade of the CTLA4 molecule by administration of anti-CTLA4 monoclonal antibody can prevent a negative signal from the B7 molecules to T- lymphocytes, thereby increasing T-cell reactivity towards tumor cells. The CD28/CTLA4-B7 costimulatory pathway is thus an important target for manipulation of anti-tumor directed T-lymphocyte responses.

---------- costimulatory antibodies ----------

9/7/36 (Item 19 from file: 73)
DIALOG(R)File 73:EMBASE

07738119 EMBASE No: 1999220681
Interaction between B.7 and CD28 costimulatory molecules is essential for the activation of effector function mediating spontaneous tumour regression
Rao K.L.; Varalakshmi Ch.; Kumari A.L.; Khar A.
A. Khar, Ctr. for Cellular/Molecular Biology, Uppal Road, Hyderabad 500 007 India
Scandinavian Journal of Immunology (SCAND. J. IMMUNOL.) (United Kingdom) 1999, 49/6 (633-640)
CODEN: SJIMA ISSN: 0300-9475
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 47

The spontaneous regression of a rat histiocytoma, AK-5, is mediated by activated natural killer cells through antibody-dependent cellular cytotoxicity. In addition to the Fc-FCR interaction between the target and the effector cells demonstrated previously, we show the participation of

costimulatory molecules B7 and CD2[redacted] the efficient killing of the tumour cell. Blockade of the costimulatory interaction in vivo using anti-CD28 led to increased tumour growth and a suppressed cytokine response. Anti-CD28 antibody administration in vivo also diminished the cytotoxic potential of NK cells against AK-5 cells in vitro. Our studies also demonstrate the expression of B7.1 and B7.2 antigen on AK-5 tumour cells. The cytotoxic activity of natural killer cells was significantly inhibited when the effector/target cells were cultured in the presence of antibodies raised against B7.1, B7.2 and CD28. Administration of anti-CD28 in vivo also affected the efficiency of the formation of effector/target conjugates in vitro. Similarly, anti-CD28 injections affected expression of the adhesion molecules LFA 1 and ICAM 1 by splenocytes. Administration of anti-B7.1 and B7.2 antibodies in AK-5 tumour-bearing animals showed a differential response. The cytotoxicity of natural killer cells was significantly inhibited after anti-B7.2 administration, suggesting the preferential participation of B7.2 molecules in vivo. These observations suggest an important role for B7-CD28 interaction in AK-5 tumour regression.

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---------- costimulatory antibodies ----------

9/7/31 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE

11520485 EMBASE No: 2002092465
Provision of antigen and CD137 signaling breaks immunological ignorance, promoting regression of poorly immunogenic tumors
Wilcox R.A.; Flies D.B.; Zhu G.; Johnson A.J.; Tamada K.; Chapoval A.I.; Strome S.E.; Pease L.R.; Chen L.
L. Chen, Department of Immunology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905 United States
AUTHOR EMAIL: chen.lieping@mayo.edu
Journal of Clinical Investigation (J. CLIN. INVEST.) (United States) 2002, 109/5 (651-659)
CODEN: JCINA ISSN: 0021-9738
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 45

Treatment of advanced, poorly immunogenic tumors in animal models, considered the closest simulation available thus far for conditions observed in cancer patients, remains a major challenge for cancer immunotherapy. We reported previously that established tumors in mice receiving an agonistic mAb to the T cell costimulatory molecule 4-1BB (CD137) regress due to enhanced tumor antigen-specific cytotoxic T lymphocyte responses. In this study, we demonstrate that several poorly immunogenic tumors, including C3 tumor, TC-1 lung carcinoma, and B16-F10 melanoma, once established as solid tumors or metastases, are refractory to treatment by anti-4-1BB mAb. We provide evidence that immunological ignorance, rather than anergy or deletion, of tumor antigen-specific CTLs during the progressive growth of tumors prevents costimulation by anti-4-1BB mAb. Breaking CTL ignorance by immunization with a tumor antigen-derived peptide, although insufficient to stimulate a curative CTL response, is necessary for anti-4-1BB mAb to induce a CTL response leading to the regression of established tumors. Our results suggest a new approach for immunotherapy of human cancers.

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---------- costimulatory antibodies ----------

9/7/29 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE
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11600847 EMBASE No: 2002172884
Tuning tumor-specific T-cell activation: A matter of costimulation?
Abken H.; Hombach A.; Heuser C.; Kronfeld K.; Seliger B.
H. Abken, Tumorgenetik, Klinik I fur Innere Medizin, Universitat zu Koln, D-50931 Koln Germany
AUTHOR EMAIL: hinrich.abken@medizin.uni-koeln.de
Trends in Immunology (TRENDS IMMUNOL.) (United Kingdom) 01 MAY 2002, 23/5 (240-245)
CODEN: TIRMA ISSN: 1471-4906
PUBLISHER ITEM IDENTIFIER: S1471490602021804
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 54

The stimulation of a specific antitumor immune response, involving the recruitment of T cells and induction of T-cell effector functions, is an attractive possibility for cancer immunotherapy. In the past few years, advances in our understanding of the mechanisms of T-cell activation and costimulation have provided the basis for strategies to enhance antitumor immunity and break tolerance. These strategies include the equipment of tumor cells with costimulatory molecules such as B7, blockade of inhibitory signals on T cells (e.g. through cytotoxic T-lymphocyte antigen 4) and grafting of T cells with antigen-triggered, recombinant costimulatory receptors. Combining antigen-triggered activation with appropriate costimulatory pathways will lead to novel approaches to improve the efficacy of T-cell-mediated adoptive immunotherapy of malignant diseases.

---------- costimulatory antibodies ----------

9/7/28 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE
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11649529 EMBASE No: 2002220234
Targeting T cell costimulation in autoimmune disease
Stuart R.W.; Racke M.K.
R.W. Stuart, Department of Neurology, Center for Immmunology, University of Texas Southwestern, 5323 Harry Hines Blvd., Dallas, TX 75390-9036 United States
AUTHOR EMAIL: Michael.Racke@utsouthwestern.edu
Expert Opinion on Therapeutic Targets (EXPERT OPIN. THER. TARGETS) (United Kingdom) 2002, 6/3 (275-289)
CODEN: EOTTA ISSN: 1472-8222
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 120

Many factors contribute to the pathogenesis of autoimmune diseases. Targets for treating such debilitating diseases will become more apparent by understanding the nature of immune activation. This review examines the possibility of targeting costimulation and discusses the molecules found on the T cell and the antigen-presenting cell (APC) that participate in T cell activation. Although new molecules continue to be discovered, the functions of B7-1 (CD80), B7-2 (CD86), CD28, cytotoxic T lymphocyte antigen 4 (CTLA-4), inducible costimulator (ICOS), programmed death 1 (PD-1), OX 40

(CD134) and CD40 ligand (CD40L, C[redacted]54) are now sufficiently understood that immunologists are targeting them to manipulate T cells to slow the progression of autoimmune diseases or treat tumours through the increase in T cell activation. CD28, ICOS, OX 40 and CD40L are considered the costimulatory molecules that increase T cell activation. However, ICOS and OX 40 appear to act on memory cells while CD28 is predominantly a naive T cell activator. Most therapies in the treatment of autoimmunity that target these molecules work through blockade of their function with receptor specific immunoglobulin (Ig). CTLA-4 and PD-1 are considered to be the inhibitory T cell costimulators. While stimulating CTLA-4 has not been a widely used therapy, using soluble CTLA-4Ig to block B7 and disrupt the B7/CD28 pathway is fairly common. The majority of therapeutic use for PD-1 stems from targeting PD-1 with its natural ligand. It is hoped that therapies targeting costimulation may provide a means of conserving the patient's normal T cell repertoire and immune function whilst eliminating or suppressing autoreactive T cells and thus provide a more efficient means to treat autoimmune disease.

_____immunogenicity
---------- costimulatory antibodies ----------

9/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12748448 BIOSIS NO.: 200000502071
Therapeutic efficacy of OX-40 receptor antibody depends on tumor immunogenicity and anatomic site of tumor growth.
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JOURNAL: Cancer Research 60 (19):p5514-5521 October 1, 2000
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DOCUMENT TYPE: Article
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SUMMARY LANGUAGE: English

ABSTRACT: The OX-40 receptor (OX-40R) is a cell surface glycoprotein of the tumor necrosis factor receptor family that is expressed primarily on activated CD4 T cells. Engagement of OX-40R by the OX-40 ligand (OX-40L) is known to costimulate the production of cytokines by activated T lymphocytes and to rescue effector T cells from activation-induced cell death. It was previously reported that in vivo ligation of OX-40R by administration of OX-40L:immunoglobulin fusion protein or OX-40R monoclonal antibody (mAb) resulted in a significant prolongation of survival of tumor-bearing mice in four histologically distinct solid tumors. In this study, we demonstrate that the therapeutic efficacy of OX-40R mAb was influenced by the tumor burden, the intrinsic immunogenicity of the tumor as well as by the histological site of tumor growth. Whereas subdermal and intracranial growth of weakly immunogenic MCA 203 and MCA 205 sarcomas and GL261 glioma were susceptible to the mAb treatment, established pulmonary MCA 205 metastases were refractory to the same regimen of treatment. Furthermore, the mAb administration had no impact on the growth of the poorly immunogenic B16/D5 melanoma. Tumor regression mediated by OX-40R mAb was dependent on the participation of both CD4 and CD8 T cells and as a result of tumor rejection, a long-term tumor-specific immunity was established. Analysis of tumor-infiltrating T cells revealed the presence of a far greater number of OX-40R+ T cells of both CD4 and CD8 phenotypes in the intracranial immunogenic GL261 glioma

than that in the poorly immunogenic B16/D5 melanoma. These results suggest that ligation of OX-40R on activated T cells in situ in the tumor may provide a necessary costimulatory signal to augment immune responses leading to tumor regression and immunological memory.

_____model

---------- costimulatory antibodies ----------

12977634 BIOSIS NO.: 200100184783
Divergent effects of 4-1BB antibodies on antitumor immunity and on tumor-reactive T-cell generation.
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SUMMARY LANGUAGE: English

ABSTRACT: 4-1BB is an inducible receptor-like protein expressed rapidly by both CD4 and CD8 T-cells after activation. 4-1BB cross-linking, either by binding to 4-1BBL or by antibody ligation, delivers a costimulatory signal to enhance T-cell activation and proliferation. Previous studies have demonstrated that the administration of 4-1BB monoclonal antibodies (mAbs) induces antitumor immune responses. In the current study using several murine tumors, we examined the systemic effects of 4-1BB mAb on the growth of s.c., intracranial (i.e.), and pulmonary metastases. In addition, the effects of 4-1BB mAb on the generation of antitumor effector T cells were examined. Treatment of 3-day i.c. MCA 205 sarcoma and GL261 glioma with the antibody resulted in prolongation of survival and cure of disease in some mice, whereas only minimal therapeutic effects were observed in established s.c. and pulmonary tumors. No antitumor effects against the poorly immunogenic B16/D5 melanoma were observed. Interestingly, successful treatment of i.c. tumors induced concomitant regression of s.c. tumors. Experiments using severe combined immunodeficient mice and mice depleted of either CD4 or CD8 T cells demonstrated T-cell dependence of the antitumor effects. For generation of effector T cells in the tumor-draining lymph nodes (LNs), administration of 4-1BB mAb had adverse effects, despite the apparent hypertrophy of the LNS. During in vitro activation of tumor-draining LN T cells with anti-CD3 and interleukin 2, the 4-1BB mAb augmented proliferation, resulting in an increase in CD8 T cells. However, they were less therapeutic than not treated LN cells. In adoptive immunotherapy, the coadministration of 4-1BB mAb enhanced the therapeutic efficacy. These results thus demonstrate the limits and potential advantages of 4-1BB antibody interactions with anti-tumor T cells in vivo and in vitro and suggest that therapeutic interactions of the antibody may be used in a variety of immunotherapeutic approaches.

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---------- costimulatory antibodies ----------

9/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

14025085 BIOSIS NO.: 200300019
Costimulatory molecule-targeted antibody therapy of a spontaneous autoimmune disease.
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JOURNAL: Nature Medicine 8 (12):p1405-1413 December 2002 2002
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ISSN: 1078-8956
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LANGUAGE: English

ABSTRACT: Humans and mice deficient in Fas, a tumor necrosis factor (TNF)-receptor family member, cannot induce apoptosis of autoreactive cells, and consequently develop progressive lymphoproliferative disorders and lupus-like autoimmune diseases. Previous studies have shown that short-term administrations of agonistic monoclonal antibodies against CD137, another TNF-receptor family member, activate T cells and induce rejection of allografts and established tumors. Here we report that treatment with an agonistic monoclonal antibody to CD137 (2A) blocks lymphadenopathy and spontaneous autoimmune diseases in Fas-deficient MRL/lpr mice, ultimately leading to their prolonged survival. Notably, 2A treatment rapidly augments IFN-gamma production, and induces the depletion of autoreactive B cells and abnormal double-negative T cells, possibly by increasing their apoptosis through Fas- and TNF receptor-independent mechanisms. This study demonstrates that agonistic monoclonal antibodies specific for costimulatory molecules can be used as novel therapeutic agents to delete autoreactive lymphocytes and block autoimmune disease progression.

---------- costimulatory antibodies ----------

14201479 BIOSIS NO.: 200300195508
Therapeutic vaccination with tumor cells that engage CD137.
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DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Therapeutic cancer vaccination is based on the finding that tumors in both humans and experimental animals, such as mice, express potential immunological targets, some of which have high selectivity for cancer cells. In contrast to the successful vaccination against some infectious diseases, where most vaccines induce neutralizing antibodies that act prophylactically, the aim of therapeutic cancer vaccines is to treat established tumors (primarily micrometastases). Since most tumor-destructive immune responses are cell-mediated, therapeutic cancer vaccination needs to induce and expand such responses and also to overcome "escape" mechanisms that allow tumors to evade immunological destruction. Tumor antigens (as with other antigens) are presented by "professional" antigen-presenting cells, most notably dendritic cells (DC). Therefore DC

that have been transfected or "pulsed" to present antigen provide a logical source of tumor vaccines, and some encouraging results have been obtained clinically as well as in preclinical models. An alternative and more physiological approach is to develop vaccines that deliver tumor antigen for in vivo uptake and presentation by the DC. Vaccines of the latter type include tumor cells that have been modified to produce certain lymphokines or express costimulatory molecules, as well as cDNAs, recombinant viruses, proteins, peptides and glycolipids which are often given together with an adjuvant. Several studies over the past 5 years have demonstrated dramatic therapeutic responses against established mouse tumors as a result of repeated injections of agonistic monoclonal antibodies (MAbs) to the costimulatory molecule CD137 (4-1BB). However, the clinical use of such MAbs may be problematic since they depress antibody formation, for example, to infectious agents. The alternative approach to transfect tumor cells to express the CD137 ligand (CD137L) increases their immunogenicity, but vaccination with tumor cells expressing CD137L is ineffective in several systems where injection of anti-CD137 MAb produces tumor regression. Recent findings indicate that a more effective way to engage CD137 towards tumor destruction is to transfect tumor cells to express a cell-bound form of anti-CD137 single-chain Fv fragments (scFv). Notably, tumors from melanoma K1735, growing either subcutaneously or in the lung, could be eradicated following vaccination with K1735 cells that expressed anti-CD137 scFv. This was in spite of the fact that K1735, as with many human neoplasms, expresses very low levels of MHC class I and has low immunogenicity. Similar results were subsequently obtained with other tumors of low immunogenicity, including sarcoma Ag104. We hypothesize that the concomitant expression of tumor antigen and anti-CD137 scFv effectively engages NK cells, monocytes and dendritic cells, as well as activated CD4+ and CD8+ T cells (all of which express CD137) so as to induce and expand a tumor-destructive Th1 response. While vaccines in the form of transfected tumor cells can be effective, at least in mouse models, the logical next step is to construct vaccines that combine genes that encode molecularly defined tumor antigens with a gene that encodes anti-CD137 scFv. Before planning any clinical trials, vaccines that engage CD137 via scFv need to be compared in demanding mouse models for efficacy and side effects with vaccines that are already being tested clinically, including transfected DC and tumor cells producing granulocyte-macrophage colony-stimulating factor.